REMARKS

I. Status of the Claims

Claims 1-32 were originally in the application. Claims 1-25 have been cancelled. Claims 26-32, which were previously non-elected claims in U.S.S.N. 09/354,664, were previously in the application. Claims 26-32 were subject to a restriction requirement. Claims 26-28 were elected.

Earlier claims 26-27, 33-37, 39, 43, and 45 were amended and new claims 46-48 were added. In the previous Supplemental Amendment, claims 26, 40-41, and 43 were amended.

Claims 26-27, 33-37, and 39-48 are currently in the application.

II. Reiteration of the Request for a Corrected Filing Receipt

On 14 November 2003, Applicants filed a Request for Corrected Filing Receipt, but did not receive it. Most recently, Applicants reiterated their request in the Amendment filed on March 23, 2009. Applicants continue to await a revised, corrected filing receipt, as noted in the reminder requests in the Amendments filed on 28 November 2006, 13 July 2007 (copy also provided with Request for Continued Examination on 12 October 2007), 9 May 2008, March 23, 2009, and July 7, 2009.

Applicants hereby reiterate their request to receive the Corrected Filing Receipt forthwith.

III. The Rejection of Claims 26-27, 33-37, and 39-48 under 35 U.S.C. §103(a) is Traversed

The Examiner has maintained the rejection of claims 26-27, 33-37, and 39-48 under 35 U.S.C. § 103(a), alleging obviousness over Rogers et al. (Analyt. Biochem. 247: 223-227 [May 1997]; "Rogers & Burgoyne" or "Rogers") in view of Burgoyne (U.S. Patent 5,496,562) and in view of Kahn et al. (Methods Enzymol. 68: 268-280 [1979]; "Kahn"). Applicants respectfully traverse this rejection.

Applicants have already discussed these references at length. For the reasons already on record, Applicants respectfully traverse this rejection.

On behalf of the Applicants, Dr. Walter King and Applicants' undersigned representative were granted a telephonic interview by the Examiner on August 5, 2009. During the interview, the teachings of Rogers and Burgoyne were discussed with respect to the outstanding rejection under 35 U.S.C. 103(a) over Rogers, Burgoyne, and Kahn. The possibility of filing an affidavit or declaration to support the attorney arguments made in the Supplemental Amendment (p. 9), mailed July 7, 2009, was also discussed, namely:

> Applicants note that Rogers & Burgoyne describes experiments with genomic DNA. Kahn mentions how plasmid DNA can be separated from genomic DNA on the basis of its smaller size or its unique properties of it being a covalently closed circular DNA or, in other words, less complex than genomic DNA, but this reference actually teaches away from the present invention. For example, as Applicants have previously noted, plasmid DNA behaves differently from genomic DNA based on its composition and its structure. It would not be expected that less complex DNA would interact with a solid matrix in the same manner as genomic DNA, so it would not be intuitive that plasmid DNA could be isolated on a solid matrix. In point of fact, prior separation of plasmid DNA from genomic DNA is preferred, as shown in Old & Primrose and other references previously submitted by Applicants for the Examiner's consideration. Burgoyne, however, only demonstrates DNA isolation directly from cells for genomic DNA, whereas the isolation of plasmid DNA requires pre-purification prior to contact with the solid medium. It would not have been at all clear, much less a matter of reasonable expectation, that isolation of plasmid DNA directly from cells (despite the presence of genomic DNA) would be possible, particularly given the low copy numbers of some plasmids (see, e.g., Lerner & Inouye, "Low copy number plasmids regulated low-level expression of cloned genes in *Escherichia coli* with blue/white insert screening capability," Nucl. Acids Res. 18(15): 4631 (1990)). One of ordinary skill in the art would have recognized that plasmid DNA in general constitutes a small fraction of DNA in the host cell and that the situation would be exacerbated where the plasmid copy number is low. In such a situation, efficient retention and recovery would be important,

> while those of ordinary skill in the art would have considered removal of RNA and genomic DNA to have been a usual step during isolation procedures (see, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual (2nd ed.), Cold Spring Harbor Laboratory Press (Cold Spring Harbor, NY: 1989), pp. 1.1-1.11, 1.21-1.24, and 1.51). [Supplemental Amendment, p. 9 (July 7, 2009).]

In accordance with the Examiner's request, Applicants submit herewith a Supplemental Declaration of Dr. Walter King Pursuant to 37 C.F.R. 1.132 ("Supplemental Declaration"). As noted by Dr. King, plasmid vectors are small, circular molecules of double-stranded DNA:

> ....The number of copies of a particular plasmid in a cell varies from one plasmid to the next depending on the mechanism by which replication is regulated. Low copy-number plasmids are present in 1-2 copies per cell. The bacterial genome of *E. coli*, which is the most common host for plasmid vectors containing recombinant DNA segments, is approximately 4.6 million base pairs, while their corresponding plasmids, such as the ColE1 family, are about 3 orders of magnitude smaller.
>
> ....This discrepancy in mass poses a significant technical challenge in the development of a suitable matrix for the efficient recovery of plasmid DNA where the binding capacity per unit area is limited. Because one of skill in the art was dealing with a poorly understood mechanism of macromolecular binding in a dried spot, the binding capacity of such treated matrices in complex media, like bacterial cultures, is not limited to just DNA, but also proteins and other macromolecules present in the culture, which further limits the number of "available sites" on the matrix. [Supplemental Declaration, pars. 7-8.]

Dr. King notes the difference between the present invention and the recovery of previously purified plasmid in Burgoyne, namely, that the input DNA of the previously purified plasmid of Burgoyne was uniformly plasmid DNA "devoid of other macromolecules present in the original bacterial culture, whereas the present invention deals with unpurified samples including a large number of many types of macromolecules having a discrepancy of mass.

To illustrate how this mass discrepancy becomes problematic for the recovery of non-purified plasmids in a bacterial culture, Dr. King provides the following example:

> If 0.1 microgram of purified pUC19 plasmid DNA (the plasmid example used by Burgoyne) was applied to FTA® medium, this would correspond to approximately 3.4×10^{10} molecules on the paper. If 99% (Burgoyne termed "approximately 100%") of the DNA were detected, then

> approximately 1% or 3.4 x 10^8 molecules of plasmid DNA might not be detected. Conversely 0.1 microgram of E. coli DNA from a culture containing a low copy plasmid only corresponds to approximately 2 x10^7 molecules of genomic *E. coli* DNA and the same number of plasmid DNA molecules, which is more than an order of magnitude lower in target molecules than the purified plasmid scenario. In the context of finite binding capacity of any substrate where the mass of DNA is independent of genome size, ***the 1.9 x10^7 molecules of plasmid DNA which co-purified with the genomic DNA would be below the total number of plasmid DNA inputted on the paper***. [Supplemental Declaration, par. 9; all emphasis in original.]

Dr. King notes:

> ....**In situations where the mass of the plasmid is several orders of magnitude lower than that of the host DNA, the efficient recovery and detection is not at all feasible from a mass perspective.** [Supplemental Amendment, par. 10; all emphasis in original.]

Finally, he concludes that "the teachings of Rogers, Burgoyne, and Kahn, either alone or in combination, would not have suggested the present invention to one of ordinary skill in the art with any reasonable expectation of success" (Supplemental Amendment, par. 11).

Applicants respectfully draw the Examiner's attention to the Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Fed. Reg. 72(195): 57526-57535 (Oct. 10, 2007). The Patent Office has failed to show that the present invention has in any way combined prior art elements according to known methods in these three references to yield predictable results, or that this is a case of simple substitution of one known element for another to obtain predictable results or use or application of a known technique to improve a similar device in the same way. The Patent Office has not shown that the present invention is the result of predictable variation or that it resulted from the choice from a finite number of identified, predictable solutions having a reasonable expectation of success, nor has it shown that it would have been obvious to try with a reasonable expectation of success. Moreover, there is no teaching, suggestion, or motivation in Rogers & Burgoyne, Burgoyne, and/or Kahn that would have led one of ordinary skill in the art

to modify one or more of these references or to combine their teachings to result in the method of plasmid isolation directly from host cells (rather than pre-purified) as in the present invention. [See, e.g., Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, Fed. Reg. 72 (195): 57526-57535, 57529 (Oct. 10, 2007).]

With respect to MPEP 2143, the present invention is **not** a simple substitution (see, e.g., *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988)), because there would have been no reasonable expectation of success given the state of the art at the time the invention was made (as discussed above and in previous Amendments) (see also MPEP 2143.02); it is **not** the result of predictable variation or that it resulted from the choice from a finite number of identified, predictable solutions having a reasonable expectation of success, **nor** would it have been obvious to try with a reasonable expectation of success (see, e.g., *Pfizer v. Apotex*, 480 F.3d 1348, 82 USPQ2d 1321 (Fed. Cir. 2007); *Ex parte Kubin*, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007)), due to the differences in properties between genomic DNA and plasmid DNA; **nor** was there any teaching, suggestion, or motivation in Rogers & Burgoyne, Burgoyne, and/or Kahn that would have led one of ordinary skill in the art to modify one or more of these references or to combine their teachings to result in the method of plasmid isolation directly from host cells (rather than pre-purified) as in the present invention (MPEP 2143). These points were addressed by the previously filed Declaration of Dr. Walter King, filed March 23, 2009.

Therefore, it is **not** intuitive that adding the cells directly would have purified the plasmid DNA, nor would one of ordinary skill in the art have considered it obvious to try with any reasonable expectation of success given the emphasis in the art of (1) the different properties of genomic DNA vs. plasmid DNA and (2) the need, at least for some purposes, to separate the two.

In view of the foregoing, Applicants respectfully submit that remaining claims 26-27, 33-37, and 39-48 fulfill the requirements of 35 U.S.C. §103(a), and request the Examiner's reconsideration of these claims accordingly.

IV. Additional Remarks

If the Examiner has any questions, the Examiner is invited to contact Applicants' undersigned representative (617-517-5516 or 617-239-0100) to schedule a telephone interview regarding the above-referenced case.

CONCLUSION

In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

Applicants respectfully submit that no extension of time is required for the Amendment and accompanying materials. If, however, a petition for an extension of time is required, then the Examiner is requested to treat this as a conditional petition for an extension of time and the Commissioner is hereby authorized to charge our deposit account no. 04-1105 for the appropriate fee. Although it is not believed that any additional fee (in addition to the fee concurrently submitted) is required to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

Date: October 6, 2009

Kathryn A. Piffat, Ph.D. (Reg. No. 34,901)
EDWARDS ANGELL PALMER & DODGE, LLP
P.O. Box 55874
Boston, Massachusetts 02205
Telephone: 617-239-0100
Facsimile: 617-227-4420 (new)

Customer No. 21874